

REMARKS

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96 and 100 are pending. Claims 2, 3, 11-14, 28-34, 37, 64, 67, 68, 92, 93 and 101-103 are canceled. Applicants request entry of amendments to claims 4-7, 34, 37, 38, 46, 49, 50, 51, 63 and 65. The basis for the amendments can be found throughout the specification especially in the examples. Most notably claim 34 has been amended to include the subject matter of claim 103 with the subsequent canceling of claim 103. The claims not cancelled that depended from claim 103 are now amended to depend from claim 34. These amendments have been made to better clarify the claims. Claim 104 has been newly added and is supported in the specification for example starting at page 21, paragraph 80.

Rejection Under 35 U.S.C. §103(a)

Claims 2-7, 11-14, 28-34, 37, 38, 46, 49-51, 53-65, 67, 68, 72, 74-78, 92-96 and 100-103 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Elbashir *et al.*, The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888 (the Elbashir reference); Fosnaugh *et al.*, US 2003/0143732 (the Fosnaugh reference); and Morrissey *et al.*, US 2003/0206887 (the Morrissey reference). Claims 2, 3, 11-14, 28-34, 37, 64, 67, 68, 92, 93 and 101-103 have been canceled herein obviating the rejection against these claims. Applicants respectfully traverse the rejection for the following reasons.

The currently amended claims are drawn to double stranded compositions comprising first and second chemically synthesized oligomeric compounds, the first oligomeric compound is capable of hybridizing with at least a portion of the second oligomeric compound and also has complementarity to and is capable of hybridizing to a selected nucleic acid target, at least one of the first and second oligomeric compounds comprises a contiguous sequence of linked nucleosides that define an alternating motif of the formula 5'-Q(-L-Z-L-Q)_n(-L-Z)_{mn}-3' where each L is an internucleoside linking group and each Q or each Z is a β-D-deoxyribonucleoside and the other of each Q or each Z is a 2'-substituted nucleoside wherein the 2'-substituent group is other than H or OH, with each oligomeric compound being from about 18 to about 30 nucleosides in length. All claims currently depend directly or indirectly to claim 34 including claim 100 which is the only method claim. The formula 5'-Q(-L-Z-L-Q)_n(-L-Z)_{mn}-3' is newly added to better define and clarify what is being claimed

e.g. linked nucleosides that define an alternating motif and allowing for both even and odd lengths.

Applicants submit that the office action has not established a *prima facie* case of obviousness. In order to establish a *prima facie* case of obviousness, the prior art must, *inter alia*, teach or suggest each and every limitation of the claimed invention. As pointed out below the combination of the Elbashir reference, the Fosnaugh reference and the Morrissey reference do not teach or suggest every limitation of the claims.

The Elbashir reference discloses comparative data on the efficiency of siRNA duplexes having 21 nucleotides in length having 2 nucleotide 3' overhangs. They concluded that substitution of one or both siRNA strands by 2'-deoxy or 2'-O-methyl oligonucleotides abolished activity and that extensive 2'-deoxy or 2'-OCH₃ modifications reduce the ability of siRNAs to mediate RNAi. This would have logically led one of skill in the art to expect that mixing 2'-deoxy and 2'-O-methyl throughout one or both strands would have produced the same result e.g. loss of activity. The Elbashir reference therefore doesn't teach or suggest the present motif of 2'-deoxynucleosides alternating with 2'-modified nucleosides in at least one strand and in fact teaches away from such a motif.

The Fosnaugh reference discloses a double stranded motif wherein the pyrimidines of each strand are modified (purines are unmodified ribonucleosides). Nowhere is there taught or suggested a double stranded composition wherein at least one strand has alternating 2'-modified nucleosides with 2'-deoxynucleosides.

The Morrissey reference (Morrissey is also a named inventor on the Fosnaugh reference) is very similar to the Fosnaugh reference with regard to motifs. The reference describes siNA molecules wherein the strands can include phosphorothioate internucleoside linkages, modified nucleosides and also terminal capping groups. Nowhere is there taught or suggested a double stranded composition wherein at least one strand has alternating 2'-modified nucleosides with 2'-deoxynucleosides.

The Office has stated in the office action that the motivation, suggestion of all the claim limitations and a reasonable expectation of success have all been provided by the combined teachings of the Elbashir reference, the Fosnaugh reference and the Morrissey reference. Applicants disagree as nowhere in the references is there a suggestion of the

claimed motif e.g. a double stranded composition wherein at least one strand has alternating 2'- β -D-deoxynucleosides with 2'-modified nucleosides.

The Elbashir reference teaches that the use of the 2'-modification 2'-OCH₃ and 2'-deoxy in excess in one strand leads to inactivity. Clearly this reference teaches away from the claimed invention.

The Fosnaugh and Morrissey references teach few motifs essentially designed around modifying the pyrimidines of double stranded compositions. Nowhere in these references is there a suggestion of the claimed motif e.g. a double stranded composition wherein at least one strand has alternating 2'- β -D-deoxynucleosides with 2'-modified nucleosides.

The cited art is lacking a suggestion or teaching of each and every element of the presently claimed motif, therefore the Applicant submits that the Office is improperly focusing on individual elements of the claimed invention, rather than on the invention as a whole. This is not the correct analysis under 35 U.S.C. §103(a). The Office has stated that all the chemical elements of the claimed invention are shown in the prior art but has not shown how the prior art motivates or suggests the presently claimed invention **as a whole, e.g. the claimed motif**. Even if the combination of references cited by the Office were to teach the limitations of the claims, Elbashir clearly teaches away from the incorporation of the chemical modifications claimed in the instant application.

In summary, claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96 and 100 are not obvious in view of the Elbashir reference, the Fosnaugh reference and the Morrissey reference. It is believed all of the claims presently before the Office patentably define the invention over the prior art and are otherwise in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

DOCKET NO.: ISIS-5325
Application No.: 10/701,007
Advisory Action mailed: January 23, 2007

PATENT

Respectfully submitted,

Robert S. Andrews

Date: February 23, 2007

Robert S. Andrews

Registration No. 44,508

Isis Pharmaceuticals, Inc.

1896 Rutherford Road

Carlsbad, CA 92008

Telephone: (760) 603-2352

Facsimile: (760) 603-3820